UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,448	11/07/2001	David Lewis	Mirus.030.03	3784

7590 10/06/2003

Mark K. Johnson
PO Box 510644
New Berlin, WI 53151-0644

EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/007,448	LEWIS ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-16 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-16 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-16 are pending in the instant application.

Election/Restrictions

The restriction, filed July 3, 2003 is withdrawn in view of Applicants arguments during an interview conducted with Examiner Karen LaCourciere on or about September 25, 2003.

Priority

The reference to priority in the first line of the Specification is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 is indefinite because it recites the limitation "the parenchymal cell" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 1, from which claim 8 depends, makes reference to “a cell” not a “parenchymal cell”.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for a process for mixing a polynucleotide contained in a plasmid with a siRNA of said polynucleotide *ex vivo* and co-delivering said polynucleotide contained in a plasmid with said siRNA into a cell of a mammal to inhibit protein expression, does not reasonably provide enablement for a process for delivering any polynucleotide into any cell of a mammal to inhibit protein expression. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-16 encompass a process for delivering any polynucleotide into any cell of a mammal to inhibit protein expression.

The instant specification provides methodologies for inhibiting gene expression in the liver, spleen, lung, and kidney after mixing a polynucleotide contained in a plasmid with a siRNA of said polynucleotide *ex vivo* and co-delivering said polynucleotide contained in a plasmid with said siRNA via tail vein delivery and direct delivery to the bile duct.

Vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Verma (Nature, 1997 Vol. 389:239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate

regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (Science, 1995 Vol. 270:404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

The instant specification teaches inhibiting target gene expression in the liver, spleen, lung, and kidney after the co-injection of a plasmid containing the target coding region and siRNA targeted to said coding region via tail vein delivery and direct delivery to the bile duct.

Bass et al. (Nature, 2001 Vol. 411:428-429) assert that the process of effectively delivering siRNA to mammalian cells in an animal will be difficult. Bass et al. further assert that dsRNA are not sequence specific and exhibit nonspecific inhibition (see page 429, first column).

Tuma, R. (BioMedNet News and Features, Magazine, July, 2003) assert that RNA interference is a "tarted up" version of antisense (see Abstract). Tuma, R. further assert that RNA interference will run into the same problems as have antisense and gene therapies, failing to get the nucleic acid into target cells and tissues (see Abstract).

Branch (TIBS, February 1998 Vol. 23, pages 45-50) addresses the unpredictability and the problems faced in the antisense art with the following statements: "Antisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. However, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "To minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. This is a challenging quest.";

"However, their unpredictability confounds research application of nucleic acid reagents."; "Non-antisense effects are not the only impediments to rational antisense drug design. The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,..."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "Because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. Antisense compounds are no exception. As is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "Binding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. Since accessibility cannot be predicted, rational design of antisense molecules in not possible."; and, "The relationship between accessibility to oligonucleotide (ODN) binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored...It is not yet clear whether *in vitro* screening techniques...will identify ODN's that are effective *in vivo*."

Ma et al. (Biotechnology Annual Review, 2000 Vol. 5:155-196) discuss the bioavailability and cellular clearance of systemically delivered oligonucleotides. Ma et al.

discuss that for antisense action to occur, the synthetic oligonucleotide must fist enter the target cell and the cellular uptake is dependent on the cell type, the experimental conditions, the length of the oligonucleotide, the oligonucleotide sequence, and the oligonucleotide sequence and the types of incorporated modifications (see page 167, last paragraph). Ma et al. also discuss the clearance of oligonucleotides from plasma to tissues is mostly concentrated in the liver and kidney (see page 169, last paragraph). Ma et al. further discuss the majority of oligonucleotide types are excreted from the body through the urinary pathway and a minor fraction is detectable in feces (see page 170, last paragraph).

In view of the unpredictability in using siRNA *in vivo*, the specification as filed does not provide adequate guidance or examples that would show by correlation how one skilled in the art would practice the claimed invention over the scope claimed without having to engage in trial and error or undue experimentation. The specification as filed contemplates a process for delivering any polynucleotide into any cell of a mammal to inhibit protein expression. However, the instant specification provides methodologies inhibiting gene expression in the liver, spleen, lung, and kidney after mixing a polynucleotide contained in a plasmid with a siRNA of said polynucleotide *ex vivo* and co-delivering said polynucleotide contained in a plasmid with said siRNA via tail vein delivery and direct delivery to the bile duct. It is unclear how inhibiting gene expression in the liver, spleen, lung, and kidney after mixing a polynucleotide contained in a plasmid with a siRNA of said polynucleotide *ex vivo* and co-delivering said polynucleotide contained in a plasmid with said siRNA via tail vein delivery and direct delivery to the bile duct data is correlated with/or representative of a process for delivering any polynucleotide into any cell of a mammal to inhibit protein expression.

The specification does not enable delivering any polynucleotide into any cell of a mammal to inhibit protein expression as broadly claimed. The specification teaches inhibiting gene expression in the liver, spleen, lung, and kidney after mixing a polynucleotide contained in a plasmid with a siRNA of said polynucleotide *ex vivo* and co-delivering said polynucleotide contained in a plasmid with said siRNA via tail vein delivery and direct delivery to the bile duct. However, it is unclear whether the co-injection of a plasmid containing the target coding region and siRNA targeted to said coding region is actually specific to any cell or tissue since the Specification taught inhibition of gene expression in those tissues which are well known in the art to contain concentrated levels of oligonucleotides following systemic delivery (see Ma et al., for example). Furthermore, since the siRNA of the instant invention is mixed with the plasmid containing the target gene *ex vivo* prior to co-injection, it is very likely that the highly concentrated siRNA will inhibit its target gene well before it is systemically delivered.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use the claimed invention commensurate with the full scope of the claims. The current specification does not provide such guidance to delivering any polynucleotide into any cell of a mammal to inhibit protein expression as broadly claimed and one of skill in the art would have to perform undue experimentation. The quantity of experimentation required to practice the invention over the scope claimed would include the de novo determination of how to engineer and deliver any polynucleotide into any cell of a mammal to inhibit protein expression to any degree, particularly, in view of the obstacles needed to overcome to use nucleic acid therapies as

exemplified in the references discussed above. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Accordingly, limiting the scope of the claimed invention to a process for mixing a polynucleotide contained in a plasmid with a siRNA of said polynucleotide *ex vivo* and co-delivering said polynucleotide contained in a plasmid with said siRNA into a cell of a mammal to inhibit protein expression is proper.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 8, 13, and 15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over 1, 2, 6, 7, and 8 of U. S. Patent No. 6,379,966 ('966). Although the conflicting claims are not identical, they are not patentably distinct from each other because a process for delivering a polynucleotide into a cell of a mammal to inhibit protein expression comprising inserting the polynucleotide into a vessel in a

mammal, wherein vessel permeability is increased by increasing pressure against vessel walls, wherein increasing the pressure consists of increasing a volume, wherein increasing the volume consists of inserting the polynucleotide in solution in the vessel, and wherein the cell is a liver cell as instantly claimed is encompassed in the process for delivering a polynucleotide complexed with a compound into a extravascular parencymal cell of a mammal comprising inserting the polynucleotide into a mammalian blood vessel, increasing permeability of the blood vessel, wherein increasing the permeability consists of increasing pressure against the blood vessel walls, wherein increasing the pressure consists of increasing a volume of fluid within the vessel as recited in ('966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 8, 13, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Makino et al. (Hypertension, 1998 Vol. 31:1166-1170).

Claim 1 is drawn to a process for delivering a polynucleotide into a cell of a mammal to inhibit protein expression, comprising making a polynucleotide that is complementary to a nucleic acid sequence, inserting the polynucleotide into a vessel and delivering the polynucleotide to the cell. Claims 2-6, 8, 13, 15 are dependent on claim 1 and include all the limitations of claim 1 and provide the further limitations, wherein vessel permeability is

increased by increasing pressure against vessel walls by increasing a volume of fluid within the vessel, wherein the vessel consists of a tail vein and wherein the cell is a liver cell and wherein the pressure increases extravascular volume.

Makino et al. disclose the intravenous injection with antisense oligodeoxynucleotides against angiotensinogen into SHR via the tail vein (see Abstract). Makino et al. further disclose the synthetic oligonucleotides were purified, dried, and resuspended in Tris-EDTA. Asialoglycoprotein-poly(L)lysine was then added to the oligonucleotides with vigorous mixing. This solution was incubated, dialyzed against saline, filtered and electrophoresed through 2% agarose. Those antisense oligonucleotide complex conjugated with the asialoglycoprotein-poly(L)lysine retained in the well were intravenously injected via the tail vein (see page 1167, first column, for example). Makino et al. further disclose that after intravenous injection of oligonucleotide complex conjugated with the asialoglycoprotein-poly(L)lysine, mRNA levels of angiotensinogen were decreased from liver tissues specimens (see Figure 5).

The term "vessel" is interpreted broadly such that administering the oligonucleotide complex conjugated with the asialoglycoprotein-poly(L)lysine via tail vein is equivalent to inserting the polynucleotide into a vessel as claimed. Injection into the tail vein with oligonucleotide complex conjugated with the asialoglycoprotein-poly(L)lysine is equivalent to increasing vessel permeability, by increasing pressure against vessel walls, increasing a volume of fluid within the vessel, and increasing extravascular volume as claimed because the method of intravascular injection would inherently increase pressure in the area of injection and at the time of injection. The pressure against the vessel walls would inherently be increased because the needle used is external to the tail vein. The oligonucleotide complex conjugated with the

asialoglycoprotein-poly(L)lysine administered via tail vein of Makino et al. reached the liver because asialoglycoprotein-poly(L)lysine are carrier molecules targeted to the liver and the use of this carrier molecule can be successfully used to regulate liver gene expression (see page 1166, second column, for example and Figure 5).

Thus, Makino et al. anticipate claims 1-6, 8, 13, and 15.

Claims 1-5, 9, 10, 13, 14, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Wianny et al. (Nature Cell Biology, 2000 Vol. 2:70-75).

Claim 1 is drawn to the invention as described above. Claims 2-5, 9, 10, 13, 14, and 15 are dependent on claim 1 and include all the limitations of claim 1 and provide the further limitations, wherein vessel permeability is increased by increasing pressure against vessel walls by increasing a volume of fluid within the vessel, wherein the cell is a liver cell, wherein the pressure increases extravascular volume or organ volume and, wherein the polynucleotide consists of dsRNA.

Wianny et al. disclose dsRNAs diluted in water and microinjected into the cytoplasm of oocytes and embryos of mice (see page 74, first and second columns, for example). Wianny et al. further disclose that some blastocytes derived from zygotes injected with dsRNAs were transferred into the uteri of pseudopregnant mice (see page 74, second column, for example and page 72, first column).

The term "vessel" is interpreted broadly such that transferring the zygotes injected with dsRNA into the uteri is equivalent to inserting the polynucleotide into a vessel as claimed. Transferring the zygotes injected with dsRNA into the uteri is equivalent to increasing vessel

permeability, by increasing pressure against vessel walls, increasing a volume of fluid within the vessel, increasing extravascular volume, and organ volume as claimed because the method of transferring the zygotes injected with dsRNA into the uteri would inherently increase pressure in the area of microinjection and at the time of transferring. The pressure against the vessel walls would inherently be increased because the microinjection needle used is external to the uteri and injecting an increased volume of solution into the uteri would increase volume and pressure against the vessel walls.

Therefore, Wianny et al. anticipate claims 1-5, 9, 10, 13, 14, and 15.

Conclusions

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
September 29, 2003

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER